HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2021 May 10.

Published in final edited form as:

Drug Alcohol Depend. 2019 November 01; 204: 107536. doi:10.1016/j.drugalcdep.2019.06.038.

Impact of a community-based naloxone distribution program on opioid overdose death rates

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Abstract

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Background: In August 2013, a naloxone distribution program was implemented in North Carolina (NC). This study evaluated that program by quantifying the association between the program and county-level opioid overdose death (OOD) rates and conducting a cost-benefit analysis.

Methods: One-group pre-post design. Data included annual county-level counts of naloxone kits distributed from 2013-2016 and mortality data from 2000-2016. We used generalized estimating equations to estimate the association between cumulative rates of naloxone kits distributed and annual OOD rates. Costs included naloxone kit purchases and distribution costs; benefits were quantified as OODs avoided and monetized using a conservative value of a life.

Results: The rate of OOD in counties with 1-100 cumulative naloxone kits distributed per 100,000 population was 0.90 times (95% CI: 0.78, 1.04) that of counties that had not received kits. In counties that received >100 cumulative kits per 100,000 population, the OOD rate was 0.88 times (95% CI: 0.76, 1.02) that of counties that had not received kits. By December 2016, an estimated 352 NC deaths were avoided by naloxone distribution (95% CI: 189, 580). On average, for every dollar spent on the program, there was $2,742 of benefit due to OODs avoided (95% CI: $1,237, $4,882).

Conclusions: Our estimates suggest that community-based naloxone distribution is associated with lower OOD rates. The program generated substantial societal benefits due to averted OODs. States and communities should continue to support efforts to increase naloxone access, which may include reducing legal, financial, and normative barriers.

Keywords

naloxone; opioid; narcotic; harm reduction; overdose

1. Introduction

Between 1999 and 2017, nearly 400,000 people died from an opioid overdose in the United States, with the annual number of opioid overdose deaths (OOD) rapidly increasing across this period (Hedegaard et al., 2018). In 2017, the number of OODs was six times higher than in 1999. The trend in North Carolina (NC) has similarly demonstrated a sharp increase, and in the last three years (2014-2017) the annual number of OODs doubled from 962 to 2,006 (NC DHHS, 2018). The most recent wave of the opioid crisis has been characterized by large increases in overdoses caused by highly potent synthetic opioids, such as fentanyl (CDC, 2018).

As this public health crisis has escalated, a variety of programmatic and policy strategies have been employed (e.g., prescribing guidelines, drug take back programs). Innovative community-based OOD prevention programs have constituted a critical piece of the response, and one key component is naloxone distribution (Wheeler et al., 2015). Naloxone is an opioid antagonist that can rapidly reverse an overdose by binding to opioid receptors and blocking the effects of other opioids. Naloxone is safe and highly effective (Kim et al., 2009).

In NC, a community-based naloxone distribution program, led by the NC Harm Reduction Coalition (NCHRC), was implemented in August 2013, following passage of a law designed to increase naloxone access (Gen. Stat. §90-12.7). NCHRC's naloxone distribution program is managed by an Overdose Prevention Program Coordinator and operates through an extensive network of volunteers (currently more than 130 active volunteers) and outreach workers, who distribute naloxone kits throughout the state. Distribution is prioritized for populations at high risk for overdose, including active injection drug users, individuals receiving medication assisted treatment, formerly incarcerated persons with a history of opioid use, and individuals engaged in sex work. NCHRC staff and volunteers train those who receive naloxone kits on how to recognize, respond to, and reverse an opioid overdose. They also provide education on NC's Good Samaritan law (Gen. Stat. §90-12.7), which protects persons who experience an overdose or persons who witness an overdose and seek help from prosecution for possession of small amounts of drugs, paraphernalia, or underage drinking. NCHRC distributes several naloxone formulations approved by the Food and Drug Administration. The vast majority of naloxone kits distributed by the NCHRC contain two syringes and two vials containing 0.4 mg of injectable naloxone. NCHRC also distributes naloxone auto-injectors and the nasal formulation of naloxone, though in very limited quantities. As of February 2019, more than 100,000 naloxone kits had been distributed by NCHRC throughout the state (NC DHHS, 2019).

Early evidence, outside of NC, indicates that naloxone distribution programs may be associated with decreases in OOD rates (Davidson et al., 2015; Walley et al., 2013). However, most studies that have evaluated community-based naloxone programs have largely focused on process measures of program impact (e.g., number of community members trained in naloxone administration, amount of naloxone distributed and used, knowledge gained from naloxone training, ambulance calls for overdoses) (Bennett et al., 2018; Bennett and Holloway, 2012; Doe-Simkins et al., 2009; EMCDDA, 2015; Galea et al., 2006; Gaston et al., 2009; Green et al., 2008; McAuley et al., 2017; McDonald and Strang, 2016; Piper et al., 2008; Strang et al., 2008; Tobin et al., 2009; Wagner et al., 2010; Williams et al., 2014). Of the few studies that have examined impacts on OOD rates (Davidson et al., 2015; Walley et al., 2013), no research has been conducted during the most recent "wave" of the opioid crisis (i.e., large increases in overdoses involving fentanyl and other highly potent synthetic opioids) (CDC, 2018), and there has been little research examining the cost-benefit or cost-effectiveness of such programs (Coffin and Sullivan, 2013). The objectives of this study were to evaluate the NC community-based naloxone distribution program by 1) estimating the association between naloxone distribution rates and OOD rates and 2) conducting a cost-benefit and cost-effectiveness analysis of the naloxone distribution program.

2. Methods

2.1 Program impact on OOD rates

To estimate the impact of a naloxone distribution program on OOD rates in NC, we used two data sources: 1) annual counts of naloxone kits distributed by the NCHRC by county from August 2013 through December 2016 and 2) mortality data obtained from the NC Vital

Statistics Office for 2000-2016. The study was approved by the University of North Carolina at Chapel Hill Institutional Review Board.

2.1.1 Exposure—Cumulative rates of naloxone kit distribution by county were calculated by summing the number of kits distributed per county through a given year and dividing by the annual county population. Consistent with prior research (Walley et al., 2013), cumulative naloxone kit distribution rates were categorized as follows: 1) 0 cumulative kits distributed; 2) 1-100 cumulative kits distributed per 100,000 population; and 3) >100 cumulative kits distributed per 100,000 population. Therefore, counties could move to different categories during the study period. Sensitivity analyses were conducted to explore the impact of alternate cutpoints (e.g., 0, 1-75, and >75; 0, 1-125, and >125); however, no meaningful differences were observed.

2.1.2 Outcome—Annual OOD rates by county were calculated by summing the number of OODs by county by year and dividing by the county population for that year. OODs were defined as any death associated with an ICD-10 code of T40.0 (opium), T40.1 (heroin), T40.2 (other opioids, commonly prescribed opioids), T40.3 (methadone), T40.4 (other synthetic narcotics, commonly fentanyl or its analogs), or T40.6 (other and unspecified narcotics). Deaths were assigned to county of residence.

2.1.3 Analysis—Consistent with prior research, we restricted the analysis to NC counties with at least five OODs each year in the period immediately preceding program implementation (2010 through 2012) (Walley et al., 2013). This restricted the analysis to 76% of the state population, residents in 38 (of 100) counties.

We calculated descriptive statistics (means and quartiles) of naloxone kits distributed and OODs by year across counties. We used Poisson regression with generalized estimating equations (GEE) to estimate measures of association (rate ratios and 95% confidence intervals) between cumulative rates of naloxone kits distributed per county-year and OOD rates per county-year (Hanley et al., 2003). Models included an offset term for the log of total population in a county per year and a first order autoregressive working correlation matrix. All models included cubic trend terms to account for potential bias due to secular trend (e.g., changes in prescribing culture, policies and programs implemented during study period).

To examine other potential sources of confounding that might impact measures of association, we developed a conceptual figure based on the extant literature and expert understanding of factors affecting naloxone distribution and OOD rates. Based on this figure, we examined the impact of potential confounders, including county age, sex, race, and poverty distributions, as well as county urbanicity, on measures of association. All differences resulted in <5% change in point estimates; therefore, we chose a more parsimonious model excluding these covariates for final presentation.

2.2 Cost-benefit analysis

We estimated benefit-cost ratios and costs per death avoided (a cost-effectiveness measure) associated with the naloxone distribution program. To estimate total costs, we summed the

average per unit price of a naloxone kit and the estimated cost of kit distribution. We used data available on naloxone kits purchased by the NCHRC between 2015 and 2016 to estimate the per unit price of a naloxone kit. In these two years, the NCHRC purchased naloxone kits at a cost of $18,000 in 2015 and $54,000 in 2016. Based on the number of kits distributed in 2015 and 2016, the average per unit price of a naloxone kit was approximately $2/kit. Based on previous research (Coffin and Sullivan, 2013), we estimated the cost associated with kit distribution (e.g., staff time, training) as $10 per kit (a table of costs by year can be found in the supplementary material*). Thus, the total estimated cost per kit was $12. Benefits were quantified by estimating the number of deaths avoided due to the program, using model-based estimates of the impact of naloxone kit distribution on OOD rates, combined with annual county populations. For each death avoided, we applied a conservative estimate of the value of a statistical life (VSL), $4.4 million (CEA, 2017). Additional information on the VSL and deaths avoided can be found in the supplementary material.*

The costs of naloxone procured by the NCHRC are low. Recognizing that some community organizations may be unable to obtain naloxone kits at such low unit costs, we conducted a sensitivity analysis, performing comparable cost-benefit and cost-effectiveness calculations using an alternative naloxone cost estimate. Specifically, we calculated the benefit-cost ratio and cost per death avoided using an estimate of $40 per kit, as reported in Gupta et al., 2016.

3. Results

Between August 2013 and December 2016, the NCHRC distributed 39,449 naloxone kits across NC. The 38 counties with at least five OODs each year between 2010 and 2012 received 80% (n=31,500) of these kits; the analysis was focused on these counties (Table 1).

Naloxone distribution was lower in 2013 (n=472 kits from Aug-Dec 2013) and 2014 (n=4,161 kits), when distribution efforts began and increased substantially by 2015 and 2016, such that more than 13,000 kits were distributed in each of these two years (Table 1). There was variation in the number and rate of kits distributed per county per year. For example, in 2016, the number of kits distributed per county ranged from 0 to 3,394 with a median count of 132 and median rate of 86 kits per 100,000 population.

Between 2000 and 2016, the rate of OODs increased from 3.5 to 14.3 per 100,000 population, a 315% increase (Figure S1). The 38 counties in this study consistently comprised 71-78% of all OODs in the state across this period. In 2016, the rate of OODs across these 38 counties was 15.1 deaths per 100,000 population, higher than the statewide rate.

3.1 Program impact on OOD rates

Controlling for secular trend, the rate of OODs in counties with 1-100 cumulative naloxone kits distributed per 100,000 population was 0.90 times (95% CI: 0.78, 1.04) that of counties that had not received kits (Table 2). Similarly, in counties that received >100 cumulative

*Supplementary material can be found by accessing the online version of this paper at 10.1016/j.drugalcdep.2019.06.038.

naloxone kits per 100,000 population, the OOD rate was 0.88 times (95% CI: 0.76, 1.02) that of counties that had not received kits.

3.2 Cost-benefit analysis

Using model-based estimates of the impact of naloxone kit distribution on OOD rates between August 2013 and December 2016 by kit distribution category, as well as county-year population data, we estimated that approximately 352 deaths (95% CI: 189, 580) were avoided during this time (Table S2). For 2015 and 2016, the years for which we had NCHRC naloxone cost data, the approximate number of deaths avoided in this specific two-year period was 255 (95% CI: 115, 454) (Table 3). Applying a conservative VSL ($4.4 million), an estimated $1.122 billion resulted from avoiding the 255 deaths in those two years.

The benefit-cost ratio was $2,742 for the 2015-2016 period. Thus, for every dollar invested in naloxone distribution, an estimated $2,742 was saved through the monetary value of death avoidance. Additionally, we calculated a cost-effectiveness measure (cost of the program per death avoided) which focuses on the number of deaths avoided rather than the value of deaths avoided. Over the 2015-2016 period, the cost per death avoided was approximately $1,605.

As a sensitivity analysis, we used a $40 per kit price, which may be closer to the cost incurred by other community-based programs. Assuming an estimated total distribution cost of $50 per kit (i.e., $40 per kit and $10 distribution cost), the benefit-cost ratio remained well in excess of 1 at $665 (95% CI: $300, $1,185). The cost per death avoided under these assumptions was $6,612 (95% CI: $3,714, $14,661).

4. Discussion

Consistent with previous findings, our estimates suggest that community-based naloxone distribution may have a protective effect on annual county OOD rates. Among NC counties with a baseline of at least five OODs annually, we found that cumulative distribution of >100 naloxone kits per 100,000 population was associated with OOD rates that were 0.88 times that of counties with no distribution (14% lower) (95% CI: 0.76, 1.02). Similarly, we found that counties with a cumulative distribution of 1-100 kits per 100,000 population were associated with OOD rates that were 0.90 times that of counties with no distribution (11% lower) (95% CI: 0.78, 1.04). The point estimates (i.e., 0.88 and 0.90) represent those values most compatible with our data, given model assumptions, while the confidence intervals provide information on the precision of these estimates.

These findings lend support to a growing base of public health literature on the benefits of naloxone distribution. Walley et al. (2013) also examined the effect of a community-based naloxone distribution program on OOD rates. They estimated that Massachusetts counties with 1-100 cumulative kits distributed per 100,000 population had OOD rates 0.73 (95% CI: 0.57, 0.91) times that of counties with no distribution, and counties with >100 cumulative naloxone kits per 100,000 population were associated with rates that were 0.54 times as high (95% CI: 0.39, 0.76). While their estimates suggested a stronger, more protective effect, there were differences between studies, including different state contexts, differences in

distribution programs, different covariate sets, and different time periods studies (with the potency of opioids consumed changing considerably across this time). Additional research by Davidson et al. (2015) examining the impact of community-based naloxone distribution programs in California also suggested a protective effect on county OOD rates.

While the U.S. opioid crisis has unique attributes in terms of cultural norms, perceptions, and types of substances available and used, research from other countries with high OOD rates should not be overlooked. In 2011, Scotland became the first country to implement a national, publically-funded take home naloxone program. Drawing on evidence from the scientific literature, including average overdose case-fatality rates and average numbers of people present at overdose events, Bird et al. (2015) estimated that in order for naloxone to be theoretically available at all overdose events, programs should aim to distribute at least 9-20 times as many naloxone kits to at-risk drug users as the number of annual overdose deaths. In 2016, the NCHRC distributed about 12 times as many kits as deaths, and our study suggests there may be a protective effect of this level of distribution on OOD rates. Additional work is needed to examine the number of kits required to maximize impact, particularly in the current U.S. setting of increasingly potent opioids.

This study is the first published research to estimate the cost-benefit of an implemented community-based naloxone distribution program. Coffin and Sullivan (2013), drawing on published studies to estimate mortality and economic outcomes that could be expected by a naloxone distribution program targeted to heroin users, previously estimated that such programs would save lives and be cost effective even under conservative assumptions. Our study estimates that, for each dollar spent on the naloxone distribution program, over $2,500 in benefits were generated by averted OODs.

This analysis is subject to limitations. First, death certificate data provide information on decedents' county of residence; however, we do not have county of death information. The extent to which these differed is unknown. Second, the extent to which our data includes the majority of naloxone available in communities during this time period is unknown. Other sources of naloxone included naloxone filled through a prescription, emergency medical services (EMS) and law enforcement administered naloxone, and naloxone available at pharmacies through the state's standing order. While we had little information on the amount of naloxone dispensed through a prescription or by EMS and law enforcement administration during this period, we know that the statewide standing order for naloxone was signed in June 2016, allowing pharmacists to dispense naloxone to anyone at risk of overdose or anyone knowing someone at risk of overdose. To assess the impact of the naloxone standing order on results, we conducted a sensitivity analyses, removing 2016 data from the analysis, and found no meaningful impact on results. Third, the analysis is ecologic in nature and could include cross-level bias (Morgenstern, 1995). Fourth, in the analysis, we use benefits and costs in their current year dollars, and we assume reversals have saved new lives. Fifth, benefits of naloxone provision could include avoided medical costs, productivity losses, and quality of life loses. Here, we focus on the value of deaths avoided using a conservative estimate of the value of a statistical life. Such benefits, however, are not returned directly to the funders of naloxone distribution programs. Finally, many rural counties were not included in this analysis, as we restricted the analysis to counties with at

least five OODs per year prior to program implementation. Further research examining program impacts according to population density is warranted.

A growing evidence base, including our study's estimates, suggests that community-based naloxone distribution may result in lower OOD rates and substantial societal benefits through prevented deaths. States and communities should continue to support efforts to broaden access to naloxone, which may include reducing financial, legal, and/or normative barriers. Naloxone distribution is a critical piece of the public health response to the persistent opioid crisis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement

The authors thank the funding organization, the National Center for Injury Prevention and Control at the Centers for Disease Control and Prevention (NCIPC/CDC), who provided funding through the Prevention for States (PfS) grant to the NC Division of Public Health (grant 5NU17CE002728). This study was funded through a subcontract to the University of North Carolina at Chapel Hill under the PfS grant. This research was also supported by R49-CE001495 to the University of North Carolina at Chapel Hill for an Injury Control Research Center from NCIPC/CDC. The authors also wish to thank the NC Harm Reduction Coalition for providing information on naloxone kits purchased and distributed.

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TABLE 1.

Total, mean, and rate of community-based naloxone kits distributed between August 2013 and December 2016 in 38 North Carolina counties [*]

	2013[^]	2014	2015	2016	Total, across all years [†]
Total number of naloxone kits distributed across 38 counties by year	472	4,161	13,537	13,330	31,500
Mean number of kits distributed per county per year (25^{th}, 50^{th} /median, 75^{th} percentiles)	12 (0, 0, 10)	110 (2, 21, 80)	356 (22, 82, 262)	351 (27, 132, 342)	207 (2, 29, 161)
Mean rate of kits distributed per 100,000 population per county per year (25^{th}, 50^{th} /median, 75^{th} percentiles)	4 (0, 0, 5)	49 (2, 15, 62)	147 (17, 66, 132)	160 (36, 86, 168)	90 (2, 21, 95)

[*] counties with at least five opioid overdose deaths per year between 2010 and 2012

[^] only August through December 2013

[†] August 2013 through December 2016

TABLE 2.

Rate ratios[*] of association between cumulative naloxone kit distribution rates and opioid overdose death rates, North Carolina,[^] 2000-2016

	Rate Ratio (95% Confidence Interval)
0 cumulative naloxone kits distributed per 100,000 population per county-year	Ref
1-100 cumulative naloxone kits distributed per 100,000 population per county-year	0.90 (0.78, 1.04)
>100 cumulative naloxone kits distributed per 100,000 population per county-year	0.88 (0.76, 1.02)

[*] Rate ratios derived from log Poisson GEE model with first order autoregressive correlation structure and adjustment for secular trend

[^] counties with at least five opioid overdose deaths per year between 2010 and 2012

TABLE 3.

Cost-benefit analysis of naloxone distribution program in North Carolina counties, 2015-2016

Year	Cost of naloxone kits	Total costs of naloxone kit distribution*	Deaths averted (95% CI)	Value of total deaths avoided, in millions (95% CI)^	Benefit-cost ratio (95% CI)	Total naloxone distribution cost per death avoided (95% CI)
2015	$18,000	$176,740	108 (62, 172)	$475.2 ($272.8, $756.8)	$2,689 ($1,544, $4,282)	$1,637 ($1,028, $2, 851)
2016	$54,000	$232,460	147 (53, 282)	$646.8 ($233.2, $1,240.8)	$2,782 ($1,003, $5,338)	$1,581 ($824, $4,386)
Total	$72,000	$409,200	255 (115, 454)	$1,122.0 ($506.0, $1,997.6)	$2,742 ($1,237, $4,882)	$1,605 ($901, $3,558)

CI= confidence interval

* includes costs of naloxone kits and staff time and training

^ using a value of a statistical life of $4.4 million